Original Article

Neuropathic Pain After Breast Cancer Treatment: Characterization and Risk Factors

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Abstract

Context. Neuropathic pain (NP) may be an important contributor to the morbidity burden of breast cancer.

Objectives. We aimed to quantify the incidence of NP in the first year after diagnosis of breast cancer and to identify its main determinants.

Methods. We performed a prospective cohort study including 506 patients with incident breast cancer, recruited at the Portuguese Institute of Oncology of Porto, and followed for one year; patients with incident NP were additionally evaluated when this condition was diagnosed and after six months, to identify chronic NP.

Results. During the first year, 156 patients were diagnosed with NP (30.8%, 95% CI 27.0−35.0). Anxiety (relative risk [RR] 1.50; 95% CI 1.06−2.13), arm symptoms (RR 1.44; 95% CI 1.02−2.05), cancer Stage III/IV (RR 2.47; 95% CI 1.66−3.66), breast-conserving surgery with axillary lymph node dissection (RR 3.13; 95% CI 1.51−6.48), mastectomy with axillary lymph node dissection (RR 2.52; 95% CI 1.25−5.11), and damaging of the intercostobrachial nerve (RR 2.05; 95% CI 1.25−3.37) were predictors of a higher risk of NP. A total of 97 patients (62.2%, 95% CI 54.4−69.4) diagnosed with NP remained symptomatic after six months.

Conclusion. NP and chronic NP were frequent in this population, being associated with anxiety and arm symptoms before breast cancer treatments and type of surgical management. These results highlight the need for monitoring the occurrence of this neurologic side effect of treatments and to develop strategies for reducing the morbidity burden of breast cancer. J Pain Symptom Manage 2017;54:877−888.

Key Words

Anxiety, breast neoplasms, neuralgia, chronic pain

Introduction

Improvements in breast cancer survival,[1] as a result of earlier diagnosis and the use of more effective treatments,[2,3] as well as the overdiagnosis and overtreatment associated with breast cancer screening,[4] highlight the importance of morbidity, including side effects of treatment, as contributors to the global burden of breast cancer. Accordingly, in the most developed countries, the years of life lived with disability already correspond to approximately half the number of years of life lost due to premature mortality due to breast cancer.[5]

Neuropathic pain (NP), defined by the International Association for the Study of Pain (IASP) as "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system,"[6] can be an important source of disability and distress in breast cancer patients already suffering from the psychological and

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medical stressors associated with diagnosis and treatment and has been considered the most important contributor to chronic breast pain.[7] However, it is not clear to what extent chronic postsurgical pain is neuropathic in character. Previous studies that assessed the frequency of NP among breast cancer patients yielded prevalence estimates ranging between 8% and 26%:[8–10] in a prospective study of women submitted to surgery, Bruce et al.[8] found a prevalence of 24% of pain of predominantly NP origin at nine months, evaluated using the Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) and the Neuropathic Pain Questionnaire (DN4); in a retrospective study including women treated for breast cancer two to six years before, Bredal et al.[9] reported the occurrence of signs of NP in 26% of the participants, according to the S-LANSS; in a cross-sectional study evaluating women after a mean time of 9.5 years after diagnosis, 9% and 18% had NP, when evaluated with the S-LANSS and the ID-Pain, respectively.[10] However, it was reported that NP screening methods fail to identify 10–20% of patients with clinically diagnosed NP, and therefore, it was suggested that despite they may offer guidance for further diagnosis, they cannot replace clinical evaluation.[11,12] To standardize diagnostic criteria in clinical and research, a grading system, to classify the certainly with which the presence of NP can be determined, was adopted by the IASP and by the European Federation of Neurological Societies in their guidelines on NP evaluation.[11,12]

A systematic review evaluating risk factors for the development of persistent pain after surgery found that, in addition to younger age, preoperative pain, intercostobrachial nerve damage during surgery, and radiotherapy, also psychological morbidities are among the most frequently reported factors associated with chronic pain after breast cancer treatment.[13] In fact, previous studies have reported an association between anxiety and depression,[8,14–17] and also quality of sleep,[14,16,17] and the occurrence of breast pain following breast cancer treatment. However, there is little information on the impact of these factors specifically in NP. A recent systematic review addressed specifically determinants of persistent NP in high-quality studies, defined based on previous published criteria that evaluated risk of bias, and only included one study that evaluated NP after breast cancer treatment.[18] Notwithstanding, data on the relation between type of surgery[10,19,20] and radiotherapy[10,19,21,22] and the occurrence of NP remain conflicting across studies.

A prospective study with a systematic neurologic evaluation of patients in different predetermined moments of the first year after breast cancer diagnosis, including a baseline evaluation pre-treatment and a clinical assessment of NP, may contribute for a better understanding of this neurologic complication. Therefore, we aimed to characterize and estimate the incidence of NP in the first year after diagnosis and to identify their main determinants.

Methods

Study Design and Data Collection

We conducted a prospective cohort study of 506 women consecutively recruited in 2012 among those with newly diagnosed breast cancer admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto, Portugal. The study methodology has been described in detail elsewhere.[23] Briefly, we consecutively selected women proposed for surgery whose follow-up would go on in the same hospital. We excluded those previously treated for cancer, submitted to breast surgery, and those scoring less than 17, or less than 16 for women older than 65 years, in the Montreal Cognitive Assessment, which was assumed to correspond to a high probability of cognitive impairment.[24]

All participants underwent neurologic evaluation, and sociodemographic and medical data were collected, at baseline (before any treatment), two weeks after surgery, three weeks after chemotherapy (if applicable), and at one year after the enrollment. In addition to these evaluations, the patients diagnosed with NP during the first year of follow-up were evaluated two more times: at the moment of NP confirmation (which falls within the one-year follow-up of the whole cohort) and six months after (which may fall outside the one-year follow-up of the whole cohort, depending on the timing of occurrence of NP). To define the chronicity of NP, a six-month follow-up was considered; this period is enough to ensure that patients had time to complete chemotherapy and radiotherapy and is in accordance with the recent Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for considering a duration of at least three months to classify NP as chronic.[25]

Incident cases of NP were identified through referral by any member of the clinical team, or during the systematic neurologic evaluations performed by experienced neurologists. Cases identified at the time of the scheduled follow-up evaluation were assigned an estimated date of onset based on information provided by the patient.

Table 1 depicts the instruments, including the questionnaires validated for the Portuguese population, used at baseline and follow-up evaluations. The evaluations were performed by trained interviewers or clinicians, as applicable. Medical data about breast

Table 1

Description of the Instruments for Evaluation of the Participants at Baseline and in the Different Moments of Follow-up, Used for the Present Analysis

Instruments Used for Evaluation	Timing of Evaluation: Baseline (Before Breast Cancer Treatment)	Timing of Evaluation: NP Diagnosis[a]	Timing of Evaluation: 6 Mo After NP Diagnosis[a]	Description of the Instrument
MoCA	✓			Test for the rapid screening of mild cognitive impairment—an intermediate clinical state between normal cognitive aging and dementia (range 0–30).
HADS	✓			Scale assessing anxiety and depression among patients during the previous week (range for anxiety and depression: 0–21). Scores greater than five indicate a case of anxiety and depression, respectively.
PSQI	✓			Index assessing sleep quality during the previous month (range 0–21). Scores greater than five indicate a case of sleep disturbance.
QLQ-BR23	✓			Scale assessing QoL in patients with breast cancer during the previous week and month; two specific subscales were used to evaluate the existence of breast and arm symptoms before treatments.
QLQ-C30	✓			Scale assessing QoL in patients with cancer during the previous week; the median value of the global health status/QoL subscale was used to define high and low global health status/QoL; the pain subscale was used to define those with pain in the previous week.
BPI		✓	✓[b]	Questionnaire evaluating the severity and the impact of pain on the patient's daily function in the last 24 hours (range for intensity and interference: 0–10); pain severity represents the mean of four items: pain at its "worst," "least," "average," and "current pain" (each of them ranging between 0 and 10).
PDI		✓	✓[b]	Index assessing pain-related disability in seven different areas of life activity (range of global score: 0–70); the median value was used as cutoff to define lower and higher disability.

NP = neuropathic pain; MoCA = The Montreal Cognitive Assessment; HADS = Hospital Anxiety and Depression Scale; PSQI = Pittsburg Sleep Quality Index; QLQ-BR23 = Breast cancer-specific module of the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer; QoL = quality of life; QLQ-C30 = Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer; BPI = Brief Pain Inventory; PDI = Pain Disability Index.

[a]Applicable only when incident NP was diagnosed in the first years of follow-up.

[b]Applicable only when NP is present at the moment of evaluation.

cancer stage and breast surgery were collected from clinical records and revised by a surgeon with experience in breast cancer surgery.

The classification system proposed by the IASP was used to classify NP;[12] NP was considered probable if pain had a distinct neuroanatomically plausible distribution and history was suggestive of relevant lesion or disease affecting the peripheral or central somatosensory system, plus negative or positive sensory signs in neurologic examination, confined to the innervation territory of the injured nervous structure. NP was considered chronic when still present six months after its diagnosis, in the same localization, and still fulfilling the IASP criteria to probable NP diagnosis, after clinical examination. Pain sensation (pin prick) was assessed with a wood cocktail-stick and light touch sensation (brush) by a piece of cotton wool, as recommended by the IASP.[12]

The pharmacologic management of NP was assessed through patients' self-report and data collected from clinical files. For each drug, data were collected on the maximum daily dose and duration of the treatment; only drugs prescribed for continued use were considered in data analysis.

Statistical Analysis

We computed cumulative incidence estimates for NP at the one-year follow-up and the corresponding 95% CIs. Kaplan-Meier failure estimates were plotted to describe the incidence over the follow-up period.

Crude and adjusted cumulative incidence ratios (RRs) and corresponding 95% CI for the relation between different characteristics of the patients and the occurrence of NP and NP with severity ≥3 in the first year after enrollment, or chronic NP and chronic NP with severity ≥3 at six months after it was first observed, were computed using Poisson regression; the variables included in each model are described in footnotes in each table with these results. Pain severity, pain interference, and pain-related disability, at the moment of NP diagnosis and after six-months of follow-up, were described according to pharmacologic treatment for NP.

Training of the interviewers and use of standardized procedures for data collection contributed to a low proportion of missing data, and no imputation was done. Statistical analysis was conducted using STATA®, version 11.2 (StataCorp, College Station, TX).

Ethics

The study was approved by the Ethics Committee of the Portuguese Institute of Oncology of Porto (CES 406/011) and all patients provided written informed consent.

Results

A total of 503 participants (99.4%) completed the one-year follow-up evaluation; one patient died and two patients abandoned the study (no reason specified). The mean (SD) of follow-up was 379.0 (28.6) days.

Patients' Characteristics

The main demographic and medical characteristics of the participants are presented in Table 2. At baseline, 35.2% of the women were younger than 50 years, 71.6% had up to nine years of education, and 24.7% were retired. A total of 53.5% were diagnosed ductal carcinoma in situ or Stage I breast cancer, 50.3% were submitted to mastectomy, 34.5% underwent axillary lymph node dissection (ALND), and for 27.9% intercostobrachial nerve damage during the surgical procedure was reported. Most patients went on to adjuvant treatment—endocrine therapy, radiotherapy, or chemotherapy.

Table 2
Demographic and Medical Characteristics of the Breast Cancer Patients ($N = 506$)

Characteristics	n (%)[a]
Age, yrs (median [P25–P75])	54.9 (47.2–63.4)
Education, yrs (median [P25–P75])	6 (4–11)
Age, yrs	
<50	178 (35.2)
≥50	328 (64.8)
Education, yrs[b]	
≤4	216 (42.7)
5–9	146 (28.9)
≥10	144 (28.5)
Retired	125 (24.7)
Cancer stage at baseline[b]	
0[c]	35 (6.9)
I	236 (46.6)
II	156 (30.8)
III	75 (14.8)
IV	4 (0.8)
Breast cancer laterality	
Left	257 (50.8)
Right	240 (47.4)
Bilateral	9 (1.8)
Breast surgery[d]	
Mastectomy	254 (50.3)
Breast-conserving	250 (49.5)
Axillary surgery[e]	
ALND	174 (34.5)
SLNB	316 (62.6)
Intercostobrachial nerve status	
Preserved	326 (64.6)
Damaged	141 (27.9)
Without information	38 (7.5)
Neoadjuvant therapy	
Chemotherapy	35 (6.9)
Adjuvant therapy[f]	
Chemotherapy	265 (52.5)
Radiotherapy[g]	367 (73.0)
Brachytherapy[g]	95 (18.9)
Endocrine therapy[g]	422 (83.9)
Immunotherapy[g]	68 (13.5)

P25–P75 = percentile 25–percentile 75; ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy.
[a]Results are preset as n (%), except if otherwise specified; data regarding treatment are not available for one patient who abandoned the study before the post-surgery evaluation.
[b]Does not sum 100.0% due to rounding.
[c]Stage 0 breast cancer corresponds to cases of ductal carcinoma in situ; the cancer stage of one patient is based on clinical information because she abandoned the study before the post-surgery evaluation.
[d]Those patients who had both mastectomy and breast-conserving surgery are reported as mastectomy; does not sum 100.0% because one patient only performed axillary surgery.
[e]Patients who had both ALND and SLNB are reported as ALND; does not sum 100.0% because 15 patients only performed breast surgery.
[f]Does not sum 100.0% because patients could be submitted to more than one type of treatment.
[g]Data are only available for the 503 patients who completed the one-year follow-up evaluation.

Incidence and Characterization of Neuropathic Pain During the First Year of Follow-up

During the first year after diagnosis, 156 patients were diagnosed with NP (30.8%, 95% CI 27.0–35.0). All cases had clinical diagnosis and were classified as probable, according to the criteria proposed by the IASP.[12]

The clinical characteristics of NP are presented in Table 3. The symptoms onset was after surgery in 71.8% of the patients. NP was localized in the arm, thoracic/breast region, and axillary region in 67.9%, 48.7%, and 45.5% of the women, respectively, and 3.2% of the patients reported symptoms in hands/feet; the latter correspond to patients also diagnosed with chemotherapy-induced peripheral neuropathy. All patients reported at least one positive neuropathic sensory symptom (pins and needles, tingling, electric shocks, or burning); 81.4% reported the presence at least of two. On neurologic examination, allodynia (pain induced by a non-nociceptive stimulus) was reported by 87.0% of the patients.

The median scores (range; percentile 25–percentile 75 [P25-P75]) in the moment of NP diagnosis were 2.5 (0.5–9.0; 1.5–3.8) for pain severity, 4 (1.0–10.0; 3.0–5.0) for the for worse pain intensity in last 24 hours, 2 (0.0–10.0; 0.0–4.0) for current pain intensity, 1.8 (0–9.4; 0.9–3.6) for pain interference, and 15 (0.0–70.0; 7.0–29.0) for pain-related disability.

Predictors of Neuropathic Pain During the First Year of Follow-up

Table 4 presents RR for the relation between different characteristics of the patients and the occurrence of NP in surgical areas during the first year after

Table 3
Clinical Characteristics of Neuropathic Pain ($n = 156$)

Characteristics	*n* (%)
Timing of pain onset	
After neoadjuvant chemotherapy	3 (1.9)[a]
After surgery	112 (71.8)
After adjuvant chemotherapy	9 (5.8)[b]
After radiotherapy	32 (20.5)[c]
Location of pain[d]	
Arm	106 (67.9)
Thoracic/breast region	76 (48.7)
Axillary region	71 (45.5)
Hands/feet	5 (3.2)
Pain characteristics	
Burning sensation	83 (53.2)
Painful cold sensation	63 (40.4)
Electric shocks sensation	67 (42.9)
Tingling sensation	84 (53.8)
Pins and Needles sensation	143 (91.7)
Numbness sensation	151 (96.8)
Itching sensation	70 (44.9)
Hypoesthesia to touch	152 (97.4)
Hypoesthesia to prick	151 (96.8)
Allodynia	87 (55.8)
Mechanical allodynia	87 (55.8)
Static mechanical allodynia	81 (51.9)
Dynamic mechanical allodynia	34 (21.8)
Thermal allodynia	12 (7.7)
Thermal allodynia to a cold stimulus	10 (6.4)
Thermal allodynia to a hot stimulus	5 (3.2)

[a]20 Patients diagnosed with neuropathic pain performed neoadjuvant chemotherapy.
[b]93 Patients diagnosed with neuropathic pain performed adjuvant chemotherapy.
[c]115 Patients diagnosed with neuropathic pain performed radiotherapy.
[d]Does not sum 100.0% because patients may have pain in more than one location.

enrollment. Older women had a significantly lower risk and those with anxiety, arm symptoms before treatments, submitted to breast-conserving surgery with ALND or mastectomy with ALND, were at greater risk of NP, regardless of its severity at diagnosis. Additionally, cancer Stage III/IV, pain at baseline, and damaging of the intercostobrachial nerve were related with higher risk of NP, although results were not statistically significant when only the cases of NP with severity score ≥3 were considered. When further adjusted for breast and arm symptoms at baseline, pain at baseline was no longer a predictor of NP (RR 1.28, 95% CI 0.88−1.87).

From the 316 patients who underwent sentinel lymph node biopsy (SLNB) without ALND, we found NP in intercostobrachial nerve territory in 35 (11.1%).

Figure 1 depicts the cumulative incidence of NP in the surgical area during follow-up by breast and axillary surgery. Patients undergoing breast-conserving surgery and SLNB had a lower risk throughout the follow-up. Patients submitted to ALND had a higher risk of developing NP one month after the procedure than those undergoing mastectomy with SLNB, and the difference became more pronounced after six months of follow-up.

Neuropathic Pain During the Six-Month Follow-up After Its Diagnosis

The mean (SD) follow-up of the subcohort of NP patients was 190.5 (24.0) days. During this period, 37.2% of the patients diagnosed with NP received pharmacologic treatment for NP; the most frequent prescriptions were gabapentin (82.8%, maximum daily dose range 200−2400 mg) and pregabalin (31.0%, maximum daily dose range: 150−600 mg). Three patients with intercostobrachial neuralgia were referred to pain consultation for nerve block. At the end of follow-up, 27.6% of patients who had been pharmacologically treated for NP were no longer under treatment; among these, the median (P25-P75) duration of treatment was 58 (30−138) days.

A total of 97 (62.2%, 95% CI 54.4−69.4) of all patients diagnosed with NP remained symptomatic for at least six months after the diagnosis. A total of 30 (30.9%, 95% CI 22.6−40.7) had NP with severity score ≥3 and 12 (12.4%, 95% CI 7.1−20.5) had NP with severity score ≥4. The median scores (range; P25-P75) for the worse pain intensity in last 24 hours and current pain intensity were 4 (1.0−9.0; 2.0−5.0) and 1 (0.0−8.0; 0.0−3.0), respectively.

As depicted in Figure 2, there was a decrease in the median scores for pain severity, pain interference, and pain-related disability, between the diagnosis of NP and the six-month follow-up among patients not submitted to pharmacologic treatment (from 2.0 to 0.4 [$P < 0.001$], from 1.1 to 0.0 [$P < 0.001$], and from 10 to 0 [$P < 0.001$], respectively). Among the patients treated pharmacologically for NP, there was also a reduction in the three scores from 3.8 to 2.1 ($P < 0.001$), from 4.3 to 1.9 ($P < 0.001$), and from 31.0 to 14.5 ($P < 0.001$). Nevertheless, among the latter the scores were higher both at diagnosis and at follow-up.

Table 5 presents RR for the relation between different characteristics of the patients and chronic NP among patients with incident NP. In the multivariable analysis, only pharmacologic treatment for NP was significantly associated with chronic NP with severity score ≥3.

From the 35 patients who underwent SLNB without ALND and were diagnosed NP in intercostobrachial nerve territory, 10 (28.6%) maintained the pain in that location at the end of follow-up (3.2% from all submitted to SLNB without ALND), and seven of those (70.0%) had NP with severity score ≥3.

Discussion

The present study provides a comprehensive assessment of the incident NP and chronic NP in the first year after breast cancer diagnosis and treatment. It has several distinctive methodologic features that

Table 4

Crude and Adjusted RR and Corresponding 95% CI for the Relation Between Different Characteristics of the Patients and the Occurrence of Neuropathic Pain or Neuropathic Pain With Severity ≥3[a] in the First Year After Enrollment ($N = 506$)

Characteristics	Patients With NP, *n* (%)	Adjusted RR (95% CI)	Patients With NP With Severity ≥3, *n* (%)	Adjusted RR (95% CI)
Age (yrs)				
<50	67 (37.6)	1 (ref.)	34 (19.1)	1 (ref.)
≥50	84 (25.6)	0.68 (0.49–0.94)	33 (10.1)	0.53 (0.33–0.85)
Education (yrs)				
≤4	56 (25.9)	1 (ref.)	24 (11.1)	1 (ref.)
5–9	50 (34.2)	1.16 (0.78–1.74)[b]	22 (15.1)	1.07 (0.58–1.98)[b]
≥10	45 (31.2)	1.07 (0.71–1.61)[b]	21 (14.6)	1.05 (0.57–1.95)[b]
Anxiety at baseline (HADS) ($n = 505$[c])				
No	73 (23.3)	1 (ref.)	27 (8.6)	1 (ref.)
Yes	78 (40.6)	1.50 (1.06–2.13)[d]	40 (20.8)	2.14 (1.26–3.63)[d]
Depression at baseline (HADS)				
No	131 (28.2)	1 (ref.)	58 (12.5)	1 (ref.)
Yes	20 (48.8)	1.21 (0.73–1.99)[d]	9 (21.9)	1.08 (0.51–2.27)[d]
Sleep disturbance at baseline (PSQI) ($n = 505$[c])				
No	52 (25.9)	1 (ref.)	18 (9.0)	1 (ref.)
Yes	99 (32.6)	0.98 (0.68–1.40)[d]	49 (16.1)	1.45 (0.82–2.57)[d]
Global health status/QoL at baseline (QLQ-C30)				
High	67 (24.8)	1 (ref.)	36 (13.3)	1 (ref.)
Low	84 (35.6)	1.21 (0.86–1.71)[d]	31 (13.1)	0.70 (0.42–1.17)[d]
General pain at baseline (QLQ-C30)				
No	57 (23.1)	1 (ref.)	24 (9.7)	1 (ref.)
Yes	94 (36.3)	1.43 (1.01–2.01)[e]	43 (16.6)	1.61 (0.95–2.72)[e]
Breast symptoms at baseline (QLQ-BR23)				
No	47 (22.5)	1 (ref.)	19 (9.1)	1 (ref.)
Yes	104 (35.0)	1.15 (0.79–1.66)[d]	48 (16.2)	1.18 (0.67–2.08)[d]
Arm symptoms at baseline (QLQ-BR23)				
No	61 (22.7)	1 (ref.)	24 (8.9)	1 (ref.)
Yes	90 (38.0)	1.44 (1.02–2.05)[d]	43 (18.1)	1.80 (1.06–3.07)[d]
Cancer stage[f]				
0/I	59 (21.8)	1 (ref.)	26 (9.6)	1 (ref.)
II	47 (30.1)	1.32 (0.89–1.94)[g]	25 (16.0)	1.53 (0.87–2.66)[g]
III/IV	45 (57.0)	2.47 (1.66–3.66)[g]	16 (20.2)	1.89 (1.00–3.56)[g]
Number of surgeries				
1	130 (30.2)	1 (ref.)	56 (13.0)	1 (ref.)
≥2	21 (28.4)	0.89 (0.55–1.44)[h]	11 (14.9)	0.92 (0.47–1.83)[h]
Surgery[i] ($n = 487$)				
BC + SLNB	31 (16.4)	1 (ref.)	10 (5.3)	1 (ref.)
M + SLNB	34 (26.8)	1.27 (0.58–2.77)[h]	19 (15.0)	1.40 (0.44–4.39)[h]
BC + ALND	22 (46.8)	3.13 (1.51–6.48)[h]	8 (17.0)	3.45 (1.10–10.86)[h]
M + ALND	63 (50.0)	2.53 (1.25–5.11)[h]	30 (23.8)	3.24 (1.23–9.29)[h]
Intercostobrachial nerve status ($n = 467$[c])				
Preserved	66 (20.3)	1 (ref.)	28 (8.6)	1 (ref.)
Damaged	68 (48.2)	2.05 (1.25–3.37)[j]	30 (21.3)	2.01 (0.98–4.11)[j]
Chemotherapy (Adjuvant + neoadjuvant)				
No	43 (21.0)	1 (ref.)	18 (8.8)	1 (ref.)
Yes	108 (36.0)	1.18 (0.74–1.89)[h,g]	49 (16.3)	1.39 (0.69–2.81)[h]
Radiotherapy[k]				
No	40 (28.8)	1 (ref.)	24 (17.7)	1 (ref.)
Yes	111 (30.2)	0.84 (0.43–1.62)[h]	43 (11.7)	0.54 (0.22–1.34)[h]

Brachytherapy[k]				
No	136 (33.3)	1 (ref.)	63 (15.4)	1 (ref.)
Yes	15 (15.8)	0.62 (0.34–1.12)[h]	4 (4.2)	0.43 (0.14–1.30)[h]
Endocrine therapy[k]				
No	25 (30.9)	1 (ref.)	10 (12.3)	1 (ref.)
Yes	126 (29.9)	0.97 (0.62–1.51)[h]	57 (13.5)	1.05 (0.53–2.07)[h]
Immunotherapy[k]				
No	132 (30.3)	1 (ref.)	60 (13.8)	1 (ref.)
Yes	19 (27.9)	0.70 (0.42–1.16)[h]	7 (10.3)	0.51 (0.23–1.15)[h]

RR = relative risk; NP = neuropathic pain; HADS = Hospital Anxiety and Depression Scale; PSQI = Pitsburg Sleep Quality Index; QoL = quality of life (the median value was used to define high and low QoL: between 0.0 and 66.0 and between 66.1 and 100, respectively); QLQ-C30 = Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer; QLQ-BR23 = breast cancer-specific module of the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer; ALND = axillary lymph node dissection; BC = breast conserving; M = mastectomy; SLNB = sentinel lymph node biopsy.

[a]The outcomes were defined as NP ($n = 151$) and NP with severity score ≥3 ($n = 67$) in surgical area, respectively.

[b]Adjusted for age.

[c]$N < 506$ due to missing data.

[d]Adjusted for age, education, anxiety, depression, sleep quality, global health status, breast symptoms previous to treatment, arm symptoms previous to treatment and breast cancer stage, as applicable.

[e]Adjusted for age, education, anxiety, depression, sleep quality, global health status, and breast cancer stage.

[f]Stage 0 breast cancer corresponds to cases of ductal carcinoma in situ.

[g]Adjusted for age and education.

[h]Adjusted for age, breast cancer stage, number of surgeries, type of surgery, chemotherapy, radiotherapy, brachytherapy, endocrine therapy, and immunotherapy, as applicable.

[i]Those patients who had both mastectomy and breast-conserving surgery are reported as mastectomy and those who had ALND and SLNB are reported as ALND; $n < 505$ because one patient was only submitted to axillary surgery and 15 patients only performed breast surgery.

[j]Adjusted for age, breast cancer stage, number of surgeries, breast surgery, chemotherapy, radiotherapy, brachytherapy, endocrine therapy, and immunotherapy, as applicable.

[k]Data are only available for patients who completed the one-year follow-up evaluation ($n = 503$).

Fig. 1. Kaplan-Meier failure estimates to describe the incidence of neuropathic pain over the follow-up period, by breast and axillary surgery ($n = 484$ [data are not depicted for 15 patients who only performed breast surgery [breast conserving], one patient who only performed axillary surgery [ALND], and for the five patients with pain in hands/feet.]). ALND = axillary lymph node dissection; SLNB = sentinel lymph node biopsy.

contribute to improve the understanding of the occurrence of this neurologic complication of cancer treatment, and to our knowledge, this is the first investigation providing this type of clinical data in Portugal. Our study adds to previous research on this topic the standardized prospective assessment of NP, using the most recent diagnostic criteria recommended by the IASP and the recent IMMPACT recommendations to classify NP as chronic.[25] Most previous studies evaluated pain in general, not describing specifically NP, or assessing NP using screening tools, such as the DN4 and the S-LANSS. However, only the examination of somatosensory functions provide supporting evidence for altered function of the nervous system and can address the issue of presence of other types of pathologic processes that cause pain, like inflammation or edema.[12] Another important methodologic strength is the nearly complete follow-up of the main cohort and a complete follow-up of the subcohort of NP patients.

Previous studies addressed the frequency of NP in breast cancer patients: a retrospective study conducted in Norway reported the presence of pain in 41% of the participants, from whom approximately one-third reported symptoms and signs of NP, according to the S-LANSS;[9] from Scotland, a prospective cohort study found an incidence of predominantly NP of 26% and 24% at four and nine months, respectively, according to S-LANSS or DN4;[8] from the U.S., a cross-sectional study reported prevalences of NP ranging from 9% to 18%, when evaluated with the S-LANSS and the ID-Pain, respectively. Despite the use of different methods and criteria to define NP or chronic NP, our study yielded similar estimates of the frequency of NP—nearly one-third of the women were

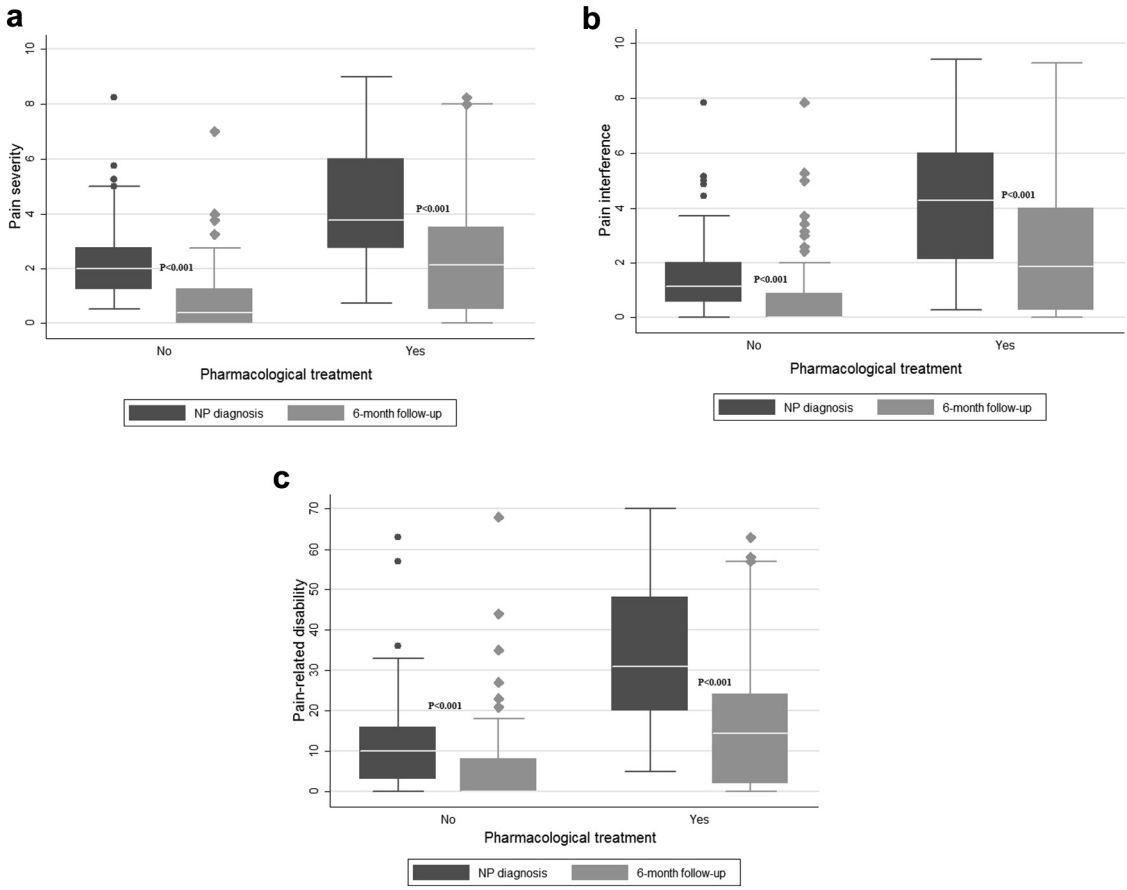

Fig. 2. Characterization of neuropathic pain, concerning pain severity, pain interference, and pain-related disability, at the moment of pain diagnosis and after six months of follow-up, according to pharmacologic treatment for neuropathic pain ($n = 156$); *P*-values computed using paired Student t-test. NP = neuropathic pain.

diagnosed with NP, from whom approximately two-thirds remained with NP six months after the diagnosis.

Despite previous studies evaluated predictors of chronic pain in breast cancer,[8,9,13] to our knowledge, this is the first addressing specifically NP, which precludes direct comparisons. Nevertheless, the fact that younger age, anxiety, arm symptoms, cancer stage III/IV, intercostobrachial nerve damage, and ALND were predictors of higher risk of NP is in accordance with previous observations for pain in general, and further supports the hypothesis that NP has an important share in the overall frequency of pain. However, it is noteworthy that only part of the patients with NP had a severity score ≥3, which is expectedly a more clinically relevant outcome. In addition to younger age, arm symptoms, and ALND, the presence of anxiety remained associated with NP when only the cases with greater severity were considered. The association between anxiety levels before cancer treatment and the occurrence of pain after breast cancer surgery was previously reported in other longitudinal studies,[8,26,27] although its relation remains poorly understood. We may hypothesize that anxious patients have lower tolerance to pain by decrease of pain threshold and, therefore, reported its occurrence more frequently.

Our study also differs from the previous ones by disentangling the determinants of NP and evolution for chronic NP; among women with an NP diagnosis, chronic NP was not significantly associated with any of the previous variables, although higher severity or interference with daily activities yielded the strongest associations, and lack of statistical significance may reflect lack of statistical power for the assessment of chronic NP determinants among those with NP. Pharmacologic treatment for NP was associated with an increased risk of chronic NP with severity score ≥3, which is likely to reflect mostly indication bias that could not be overcome by multivariable analysis. In this respect, gabapentin and pregabalin were the most frequently used drugs to treat NP, in line with the recommendations for the pharmacologic management of this condition.[28,29] Contrary to previous findings regarding chronic pain in general,[9] in our study, the frequency of chronic pain was not increased among

Table 5

Crude and Adjusted Relative Risks for the Relation Between Different Characteristics of the Patients and Chronic NP and Chronic NP With Severity ≥3[a] at 6 Months After It Was First Observed ($n = 151$)

Characteristics	Patients With Chronic NP, *n* (%)	Adjusted RR (95% CI)	Patients With Chronic NP With Severity ≥3, *n* (%)	Adjusted RR (95% CI)
Age (yrs)				
<50	43 (64.2)	1 (ref.)	18 (26.9)	1 (ref.)
≥50	52 (61.9)	0.96 (0.64–1.44)	11 (13.0)	0.49 (0.23–1.03)
Education (yrs)				
≤4	35 (62.5)	1 (ref.)	8 (14.2)	1 (ref.)
5–9	30 (60.0)	0.94 (0.56–1.59)[b]	10 (20.0)	1.06 (0.39–2.86)[b]
≥10	30 (66.7)	1.05 (0.63–1.76)[b]	11 (24.4)	1.31 (0.50–3.46)[b]
Anxiety at baseline (HADS)				
No	41 (56.2)	1 (ref.)	9 (12.3)	1 (ref.)
Yes	54 (69.2)	1.17 (0.75–1.82)[c]	20 (25.6)	2.00 (0.87–4.62)[c]
Depression at baseline (HADS)				
No	82 (62.6)	1 (ref.)	25 (19.1)	1 (ref.)
Yes	13 (65.0)	0.90 (0.48–1.70)[c]	4 (20.0)	0.87 (0.28–2.70)[c]
Sleep disturbance at baseline (PSQI)				
No	27 (51.9)	1 (ref.)	6 (11.5)	1 (ref.)
Yes	68 (68.7)	1.24 (0.79–1.96)[c]	23 (23.3)	1.74 (0.69–4.34)[c]
Global health status/QoL at baseline (QLQ-C30)				
High	41 (61.2)	1 (ref.)	15 (22.4)	1 (ref.)
Low	54 (64.3)	0.99 (0.65–1.52)[c]	14 (16.7)	0.73 (0.34–1.59)[c]
General pain at baseline (QLQ-C30)				
No	29 (50.9)	1 (ref.)	9 (15.8)	1 (ref.)
Yes	66 (70.2)	1.33 (0.84–2.10)[d]	20 (21.3)	1.23 (0.54–2.80)[d]
Breast symptoms at baseline (QLQ-BR23)				
No	24 (51.1)	1 (ref.)	6 (12.8)	1 (ref.)
Yes	71 (68.3)	1.17 (0.71–1.92)[c]	23 (22.1)	1.13 (0.43–2.95)[c]
Arm symptoms at baseline (QLQ-BR23)				
No	31 (50.8)	1 (ref.)	9 (14.8)	1 (ref.)
Yes	64 (71.1)	1.35 (0.84–2.17)[c]	20 (22.2)	1.71 (0.72–4.09)[c]
Pain severity at NP diagnosis (BPI) ($n = 147$[e])				
Lower level	41 (52.6)	1 (ref.)	5 (6.4)	1 (ref.)
Higher level	52 (75.4)	1.31 (0.79–2.17)[f]	24 (34.8)	2.49 (0.82–7.58)[f]
Pain interference at NP diagnosis (BPI)				
Lower level	41 (55.4)	1 (ref.)	3 (4.0)	1 (ref.)
Higher level	54 (70.1)	1.12 (0.62–2.04)[f]	26 (33.8)	4.50 (0.97–20.81)[f]
Pain-related disability at NP diagnosis (PDI)				
Lower level	41 (56.2)	1 (ref.)	4 (5.5)	1 (ref.)
Higher level	51 (68.9)	1.00 (0.54–1.87)[f]	25 (33.8)	1.28 (0.30–5.43)[f]
Pharmacologic treatment for NP				
No	48 (51.1)	1 (ref.)	4 (4.3)	1 (ref.)
Yes	47 (82.5)	1.61 (0.90–2.87)[g]	25 (43.9)	4.40 (1.17–16.61)[g]
Cancer stage[h]				
0/I	37 (62.7)	1 (ref.)	8 (13.6)	1 (ref.)
II	30 (63.8)	1.01 (0.62–1.67)[i]	12 (25.5)	1.59 (0.63–4.01)[i]
III/IV	28 (62.2)	0.98 (0.59–1.64)[i]	9 (20.0)	1.21 (0.45–3.25)[i]

(*Continued*)

Table 5
Continued

Characteristics	Patients With Chronic NP, *n* (%)	Adjusted RR (95% CI)	Patients With Chronic NP With Severity ≥3, *n* (%)	Adjusted RR (95% CI)
Number of surgeries				
1	82 (63.1)	1 (ref.)	25 (19.2)	1 (ref.)
≥2	13 (61.9)	1.00 (0.53–1.91)[j]	4 (19.0)	1.26 (0.38–4.16)[j]
Surgery[k] (*n* = 150)				
BC + SLNB	18 (58.1)	1 (ref.)	4 (12.9)	1 (ref.)
M + SLNB	24 (70.6)	1.21 (0.47–3.10)[j]	8 (23.5)	1.21 (0.18–8.26)[j]
BC + ALND	14 (63.6)	0.94 (0.36–2.44)[j]	6 (27.3)	0.73 (0.16–3.45)[j]
M + ALND	38 (60.3)	0.94 (0.39–2.25)[j]	11 (17.5)	0.71 (0.15–3.34)[j]
Intercostobrachial nerve status (*n* = 134[e])				
Preserved	40 (60.6)	1 (ref.)	10 (15.2)	1 (ref.)
Damaged	43 (63.2)	1.06 (0.54–2.07)[l]	16 (23.5)	1.41 (0.47–4.26)[l]
Chemotherapy (Adjuvant + neoadjuvant)				
No	27 (62.8)	1 (ref.)	4 (9.3)	1 (ref.)
Yes	68 (63.0)	1.06 (0.58–1.94)[j]	25 (23.2)	2.43 (0.66–8.89)[j]
Radiotherapy				
No	27 (67.5)	1 (ref.)	9 (22.5)	1 (ref.)
Yes	68 (61.3)	0.96 (0.43–2.16)[j]	20 (18.0)	0.51 (0.10–2.50)[j]
Brachytherapy				
No	85 (62.5)	1 (ref.)	24 (17.6)	1 (ref.)
Yes	10 (66.7)	1.15 (0.53–2.51)[j]	5 (33.3)	2.33 (0.63–8.67)[j]
Endocrine therapy				
No	16 (64.0)	1 (ref.)	5 (20.0)	1 (ref.)
Yes	79 (62.7)	1.03 (0.58–1.82)[j]	24 (19.0)	1.04 (0.38–2.82)[j]
Immunotherapy				
No	83 (62.9)	1 (ref.)	25 (18.9)	1 (ref.)
Yes	12 (63.2)	1.00 (0.53–1.91)[j]	4 (21.0)	0.96 (0.32–2.93)[j]

NP = neuropathic pain; RR = relative risk; HADS = Hospital Anxiety and Depression Scale; PSQI = Pittsburg Sleep Quality Index; QoL = quality of life (the median value was used to define high and low quality of life: between 16.6 and 58.4 and between 58.5 and 100, respectively); QLQ-C30 = Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer; QLQ-BR23 = breast cancer-specific module of the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer; BPI = Brief Pain Inventory (the median value was used to define lower and higher level of pain severity [between 0.0 and 2.5 and between 2.6 and 10, respectively] and pain interference [between 0.00 and 1.79 and between 1.78 and 10, respectively]); PDI = Pain Disability Index (the median value was used to define lower and higher level of pain-related disability [between 0 and 15 and between 16 and 70, respectively]); BC = breast conserving; SLNB = sentinel lymph node biopsy; M = mastectomy; ALND = axillary lymph node dissection.
[a]The outcomes were defined as chronic NP (*n* = 95) and chronic NP with severity score ≥3 (*n* = 29) in surgical area, respectively.
[b]Adjusted for age.
[c]Adjusted for age, education, anxiety, depression, sleep quality, global health status, breast symptoms, arm symptoms and breast cancer stage, as applicable.
[d]Adjusted for age, education, anxiety, depression, sleep quality, global health status, and breast cancer stage.
[e]*n* < 151 due to missing data.
[f]Adjusted for age, education, anxiety, depression, sleep quality, global health status, breast symptoms, arm symptoms, pain severity, pain interference, pain-related disability, breast cancer stage, number of surgeries, and type of surgery, as applicable.
[g]Adjusted for age, education, pain severity, pain interference, pain-related disability, and cancer stage.
[h]Stage 0 breast cancer corresponds to cases of ductal carcinoma in situ.
[i]Adjusted for age and education.
[j]Adjusted for age, breast cancer stage, number of surgeries, type of surgery, chemotherapy, radiotherapy, brachytherapy, endocrine therapy, and immunotherapy, as applicable.
[k]Those patients who had both mastectomy and breast-conserving surgery are reported as mastectomy and those who had ALND and SLNB are reported as ALND.
[l]Adjusted for age, breast cancer stage, number of surgeries, breast surgery, chemotherapy, radiotherapy, brachytherapy, endocrine therapy, and immunotherapy.

subjects with pain previous to treatments, although this was evaluated with a subscale of QLQ-C30 that assesses pain and disability in daily functions related to pain.

We observed only five cases of NP in patients with chemotherapy-induced neuropathy, which probably reflects the fact that at the Portuguese Institute of Oncology of Porto docetaxel is used more often in incident breast cancer than paclitaxel, which is more neurotoxic.[30]

It has been described that in just over 10% of the cases the axillary sentinel lymph node intercostobrachial nerve territory is located above the second intercostobrachial nerve and can be damaged at that localization during biopsy in approximately 5.3% of SLNB.[31] This is consistent with our observations that 3.2% of the patients underwent SLNB without ALND, had chronic NP, but highlights the problem of sequelae secondary to overdiagnosis and overtreatment of breast cancer.[32]

Despite the contribution of the present study for an accurate characterization of NP among breast cancer patients at early stages, some limitations need to be addressed, especially regarding the external validity of the results. We evaluated essentially women with early breast cancer, which limits the generalization to patients with more advanced disease. Although all patients were selected and treated in the same institution, the Portuguese Institute of Oncology of Porto is the largest hospital providing care to oncologic patients in the north of Portugal, which receives patients referred from a wide geographical area.

In conclusion, NP and chronic NP were frequent in the first year after incident breast cancer diagnosis, being associated with anxiety and arm symptoms before breast cancer treatments, as well as factors related with the type of surgical management. These results highlight the need for monitoring the occurrence of this neurologic side effect of treatments and to develop strategies for reducing the morbidity burden of breast cancer.

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